birth.

L4 cancld

135 (amended). The method of claim 133 where said package indicates individuals who have a mother, father or close relative with a chronic immune mediated disorder may be at risk for developing said chronic immune mediated disorder.

136 (amended). The method of claim 135 where said chronic immune mediated disorder is diabetes.

138 (amended). The method of claim 137 where said screening comprises comparing the incidence of the disorder in a treatment group of humans receiving said vaccine according to a first immunization schedule with the incidence of the disorder in a control group of humans.

139 (amended). The method of claim 138 in which the control group did not receive the vaccine.

L5

140 (amended). The method of claim 138 in which the control group received the vaccine according to a second and different immunization schedule.

141 (amended). The method of claim 138 in which the difference in incidence between the treatment and control groups is calculated.

142 (amended). The method of claim 141 in which the statistical significance of said difference is calculated.

143 (amended). The method of claim 137 in which the vaccine is publicly distributed, accompanied by said labeling.

REMARKS

The purpose of this paper is to (1) correct typographical errors, and (2) submit conclusive new evidence on the issue of enablement.

1. On page 105, applicant presents table IV, which purports to show the "Cumulative Incidence of Type I diabetes Mellitus in "Danish Military Recruits age 18". This table is discussed on page 97, and the reference to "Danish" appears at line 16.

However, it is bracketed by reference to the Netherlands at page 97, line 8, and page 98, lines 10 and 23.

As indicated at page 105, line 29, the data is derived from Diabetologia, 35:139-42 (1992), which by virtue of page 99, lines 22-27 is incorporated by reference. Referring to that paper, a copy of which is enclosed, it is immediately evident that the table IV data was for Dutch, not Danish military recruits. The specification at pages 97 and 105 has been amended accordingly.

2. In the course of drafting an appeal brief in response to the final rejection, Counsel realized that the dependencies of claims 131-136 and 138-143 were off by three. This was evident from a comparison of, e.g., claims 131-136 with claims 127 and 130, and 138-143 with 134 and 137. The errors in dependencies have been corrected.

3. Substitute amendment "A" cancelled claims 19, 153-158, and 260-265. However, Applicants' intent was to cancel 153-258, as is evident from the remarks. This amendment corrects the error.

4. The foregoing amendments correct typographical errors in the specification and claims, and were not earlier presented because the errors were recognized only after the final rejection was mailed. Hence 37 CFR §1.116(c) is satisfied.

5. Most importantly, there is new evidence on the issue of enablement.

The Examiner's prima facie case for nonenablement relies on various epidemiological studies, notably those reviewed in "PIDJ", and those listed on pp. 7-8 of the February 21, 2001 rejection. Applicant's rebuttal case for enablement rested on

(1) human epidemiological data, including pp. 89 to 105 in the specification, and the HiB data set forth in the Classen & Classen "Clustering of Cases" and "Large decline" articles submitted with the August 17, 2001 amendment; and

(2) animal data, including Examples 1 to 5 of the specification.

Since the final rejection, the "Clustering of Cases" article has been published in a peer reviewed journal, and an independent epidemiological study (Sanjeevi) supportive of applicant's conclusion has been published. Other new, relevant articles have been published, too.

Hence, we submit a declaration from Dr. Classen which prevents a comprehensive overview of the "competing" studies, and supporting exhibits. Those exhibits were (1) previously submitted, (2) not published prior to the November 5, 2001 final rejection, (3) responsive to points raised by the final rejection, or (4) newly discovered by applicant or applicant's counsel. Hence, 37 CFR §1.195 is satisfied.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: _____
Iver P. Cooper
Reg. No. 28,005

Enclosure
-Declaration (II) of Dr. Bart Classen, with Exhibits

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Paragraph beginning at line 15 of page 97 has been amended as follows:

Epidemiology data shows that in the cumulative incidence of diabetes up to the age of 18 differed significantly in [Danish] Dutch birth cohorts (Diabetologia 35:139-142, 1992). There were two significant drops in the incidence of diabetes; one was centered around 1962 when the cumulative incidence dropped to 1.1 per 1000 ($P<.05$), and the other was centered around 1966 when the cumulative incidence dropped to 1.71 per 1000. The drops are in contrast to a cumulative incidence of diabetes outside of these troughs of about 1.98 per 1000 (Table IV). The drops in 1962 and 1966 both occurred during smallpox epidemics in Europe and can best be explained by immunization of newborn infants in these periods with smallpox vaccines.

The title of Table IV of page 105 has been amended as follows:

Cumulative Incidence of Type I Diabetes Mellitus [Danish] Dutch Military Recruits Age 18

Paragraph beginning at line 19 of page 105 has been amended as follows:

Cumulative incidences of type I diabetes mellitus in [Danish] Dutch military recruits under 19 years of age are reported per 1000 recruits as recorded in the reference indicated. Statistics were calculated by the authors in the reference. The results show a statistically significant decline in the incidence of type I diabetes mellitus in the years 1961-1963 which corresponded to a smallpox epidemic. The decline in the incidence of diabetes in 1962 followed the epidemic of

1961. The incidence of diabetes also declined in 1966 during a second smallpox epidemic. The [later] latter was not statistically significant, N.S.

In the claims:

Claims 159-258 have been cancelled.

Claims 131-136 and 138-143 have been amended as follows:

131 (amended). The method of claim [127] 130 where said labeling indicates that the timing of the first administration of said vaccine may, can or has been reported to affect said incidence.

132 (amended). The method of claim [128] 131 where said labeling indicates that first administration of said vaccine before 42 days after birth may, can or has been reported to reduce the incidence.

133 (amended). The method of claim [127] 130 where said labeling indicates that first administration of said vaccine on or after 42 days after birth may, can or has been reported to increase the incidence.

134 (amended). The method of claim [129] 132 where said directions call for first administration before 42 days after birth.

135 (amended). The method of claim [130] 133 where said package indicates individuals who have a mother, father or close relative with a chronic immune mediated disorder may be at risk for developing said chronic immune mediated disorder.

136 (amended). The method of claim [132] 135 where said chronic immune mediated disorder is diabetes.

138 (amended). The method of claim [134] 137 where said screening comprises comparing the incidence of the disorder in a treatment group of humans receiving said vaccine according to a first immunization schedule with the incidence of the disorder in a control group of humans.

139 (amended). The method of claim [135] 138 in which the control group did not receive the vaccine.

140 (amended). The method of claim [135] 138 in which the control group received the vaccine according to a second and different immunization schedule.

141 (amended). The method of claim [135] 138 in which the difference in incidence between the treatment and control groups is calculated.

142 (amended). The method of claim [138] 141 in which the statistical significance of said difference is calculated.

143 (amended). The method of claim [134] 137 in which the vaccine is publicly distributed, accompanied by said labeling.